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METHOD FOR MODIFYING THE GROWTH OF FUR AND/OR HAIR AND COMPOSITIONS THAT CAN BE USED TO THAT EFFECT

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The invention concerns a treatment method for modifying the growth of fur and/or hair that essentially consists of administrating to the organism, by a topical and/or systemic route, substances selected from inhibitors or stimulators of lipoxygenases or cyclo-oxygenases, said administration being preferably done in combination with the (simultaneous, separate or spread out over time) intake by the organism, by a topical and/or systemic route, of at least one substrate, or a substrate precursor, of lipoxygenases and of cyclo-oxygenases. Depending on the substances chosen, one can either promote the growth and/or limit the loss of said fur and/or hair (use of inhibitors of lipoxygenases and/or stimulators of cyclo-oxygenases), or, on the other hand, decrease or prevent the growth of the latter (use of stimulators of lipoxygenases and/or inhibitors of cyclo-oxygenases).

The invention also concerns various compositions that can be used for the implementation of the method.

The present invention, most generally, concerns a treatment method for modifying the growth of fur and/or hair. More particularly, it concerns a method that allows the option, essentially depending on the nature of the products used for its implementation, of promoting the growth and/or limiting the loss of said fur and/or hair, or, on the contrary, the option to decrease or prevent the growth of the latter.

It also concerns various types of compositions intended notably for the implementation of said method, as well as some of their specific uses.

It is known that certain polyunsaturated fatty acids, particularly those having 20 carbon atoms, such as arachidonic acid, dihomo-γ-linolenic acid, or eicosapentanoic acid, can be transformed in vivo, due to the action of certain specific enzymes contained in live cells, particularly the epithelial cells, into certain other compounds of the eicosanoid type, which are useful for the organism.

Thus, it is known that the so-called cyclo-oxygenase enzymes generate, from the different above-mentioned fatty acids, eicosanoids of the prostaglandin and thromboxane type, and that the so-called lipoxygenase enzymes themselves are responsible for the formation of eicosanoids of the leukotriene type and other acyclic hydroxylated acids with 20 carbon atoms. A given polyunsaturated fatty acid (or substrate) can give rise to the formation of several different metabolites, depending on the nature of the enzyme with which it has reacted first, examples of such metabolites being prostaglandins and leukotrienes.

The polyunsaturated fatty acids , notably C_{20} (reactive raw materials), chosen to be metabolized under the specific action of cyclo-oxygenase and lipoxygenase enzymes, are generally taken up by the organism through the intermediary of certain foods, particularly certain natural oils of animal or plant origin; this intake can then occur either in the direct form (as is the case, for example, with arachidonic acid, which is present in egg whites), or indirectly in the form of precursor compounds (compounds that are also called "essential fatty acids," which themselves are, generally, C_{18}-C_{22} unsaturated fatty acids such as linoleic acid, α-linolenic acid and β-linolenic acid) and which will be transformed by human metabolism, according to complex mechanisms that need not be detailed here, into appropriate substrates (that is, metabolites) for cyclo-oxygenases and lipoxygenases.

However, after much research, the applicant has now found that the above described enzymatic transformations, and the different resulting reaction products, have a non-negligible influence on the mechanisms of fur and/or hair growth and that by selecting (according to techniques described below) one or the other of the two enzymatic pathways within the skin cells, cyclo-oxygenase and lipoxygenase, it was possible, quite unexpectedly and surprisingly, to substantially modify the growth of fur and/or hair.

More specifically still, it has been found by selecting the cyclo-oxygenase pathway, it was possible to promote the growth of fur and/or hair and/or to fight against their loss, and that by selecting the lipoxygenase pathway, on the other hand, it was possible to slow down and/or prevent the growth of the latter.

It has also been found that, from a practical point of view, it is possible to select a given enzymatic pathway in several different manners, as specified below. All these variants are based on the same basic principle, namely to supply to the organism, particularly the skin cells, substances intended to inhibit, or, on the contrary, to stimulate the action of cyclo-oxygenase or lipoxygenase enzymes, the selection of said substances naturally being made as a function of the desired technical effect.

Thus, if the intention is to promote the growth and/or limit the loss of fur and/or hair (or conversely if one wishes to slow down and/or prevent the growth of the latter), and given the fact that in that case, as indicated above, the cyclo-oxygenase pathway should be selected (or conversely the lipoxygenase path should be selected), then one can proceed, as desired, in at least one of the following manners: one or more inhibitors of lipoxygenases (or conversely of cyclo-oxygenases) are used, one or more stimulators or agonists of cyclo-oxygenases (or conversely lipoxygenases) are used, one or more inhibitors of lipoxygenases (or conversely cyclo-oxygenases) are used in association with one or more stimulators or agonists of cyclo-oxygenases (or conversely lipoxygenases), or one or more substances having the property of being simultaneous inhibitors of lipoxygenases (or conversely of cyclo-oxygenases) and stimulators or agonists of cyclo-oxygenases (or conversely lipoxygenases) are used.

In summary, it is therefore possible to select a given enzymatic pathway by direct stimulation of this pathway and/or by inhibition of the "reverse" pathway. The best results are generally obtained by combining the two effects.

Finally, it has also been found that particularly remarkable results were obtained, both in a treatment method to promote the growth of fur and/or hair and in a treatment method intended, on the contrary, to limit this growth, when the use of said inhibitors and stimulators or agonists of the above-mentioned enzymatic pathways was in addition, coupled with the use of at least one substrate that was directly metabolizable by the lipoxygenases and the cyclo-oxygenases and/or of at least one precursor of said substrate (synergistic effect).

All these discoveries are the foundation of the present invention.

In the following description of the present invention, the meanings of the terms are as follows:

- "substrate" suitable for lipoxygenases and cyclo-oxygenases denotes any substance that , as is, can be directly metabolized in vivo both by the lipoxygenase enzymes and the cyclo-oxygenase enzymes,

- "precursor" of a substrate for lipoxygenases and cyclo-oxygenases, any substance that can be metabolized in vivo by the organism into a substrate suitable for lipoxygenases and cyclo-oxygenases, as well as any substance inducing the formation of polyunsaturated fatty acids in live tissues, the latter formation being objectively demonstrated by gas chromatography or by any other standard technique, such as those described by Pelick et al., P23 "Analysis of lipids and lipoproteins" published by Perkins American Oil Chemist Society, Champaign, Illinois, U.S.A.,

- "inhibitor" of lipoxygenases or cyclo-oxygenases denotes any substance that allows, in vivo, the limitation or total

inhibition of the enzymatic activity of either one of these enzymes,

- "stimulator" or "agonist" of lipoxygenases or cyclo-oxygenases, denotes any substance that allows, in vivo, an increase in the enzymatic activity of either one of these enzymes; the term "agonist" must be understood to be included in the general term "stimulator,"

- "topical route," any technique for the administration of a product by the direct application of the latter to a superficial (or external) part of the body, such as skin, hair and others,

- "systemic route," any technique for the administration of a product by a route other than the topical route, for example, oral and/or parenteral.

Thus, according to a first aspect of the present invention, an in vivo method is now proposed for the modification of the growth of fur and/or hair, said method being characterized by the fact that it consists of administering to the organism, by the topical and/or systemic route(s), at least one inhibitor and at least one stimulator or agonist of lipoxygenases or of cyclo-oxygenases.

In the case where the above treatment method is intended more specifically for the promotion of the growth and/or limitation of the loss of fur and/or hair, at least one substance is used that can be an inhibitor of lipoxygenases and/or a stimulator of cyclo-oxygenases.

In the case where said method is intended, this time, more specifically to slow down and/or prevent the growth of fur and/or hair, at least one substance is used that can be a stimulator of lipoxygenases and/or an inhibitor of cyclo-oxygenases.

According to a particularly preferred embodiment of the treatment method according to the invention, the organism is additionally administered, besides said inhibitors or stimulators, at least one substrate for lipoxygenases and cyclo-oxygenases, or a precursor of said substrate. The intake of said substrate, or said precursor, can then be implemented by the topical and/or systemic route, simultaneously, separately, or spread out over time, with respect to the step of the administration of the inhibitors or stimulators of lipoxygenases or of cyclo-oxygenases.

According to another aspect of the present invention, devices are also proposed that contain several compartments or kits intended for the implementation of the above method, and in particular kits that are characterized by the fact that they comprise in a first compartment one or more inhibitors, or one or more stimulators, of lipoxygenases or of cyclo-oxygenases, and, in a second compartment, one or more substrate for lipoxygenases and/or cyclo-oxygenases and/or one or more precursors of said substrates, the compositions contained in said first and second compartment being considered here as combination compositions for a simultaneous use, a separate use, or a use spread out over time, in a treatment intended to modify the growth of fur and/or hair.

Finally, according to other aspects of the present invention, compositions or associations are now proposed, which are novel in themselves and suitable for the implementation of the method of the invention, with these different variants.

However, other characteristics, aspects, objects and advantages of the invention will become even clearer after a reading of the following description and of the different

concrete examples, which are intended to serve as nonlimiting illustrations.

To begin with, the nature of the different products and compositions that can be used in the context of the present invention (inhibitor/stimulator/substrate/precursor) will be detailed.

The inhibitory or stimulatory (or agonistic) character of a given substance with respect to the lipoxygenases or cyclo-oxygenases can classically be determined by a person skilled in the art using notably the usual biochemical tests, generally based on chromatographic analyses. Thus, these activities can be explored, for example, using the following techniques (nonlimiting list) or any other standardized technique:

- activity with respect to 5-, 12- and 15- lipoxygenases: one can cite here the method that consists in using a biological material (human polynuclear cells, hair) incubated in the presence of C14 arachidonic acid or C14 linoleic acid; the formed hydroxy acids are extracted, separated by thin layer chromatography or HPLC chromatography (Vanderhoeck, J. Y. and Bailey, J. M. in J. Biol. Chem., 1984, Vol. 259, pp. 6752-6761; Huang, M. et al. in Cancer Res., Vol. 51, pp. 813-819, 1991; Baer, A. N. and Green, F. A. in J. Lipids Res., 1993, Vol. 34, pp. 1505-1514; Ziboh, V. A. et al. in J. Invest. Dermatol., Vol. 83, pp. 248-251, 1984).

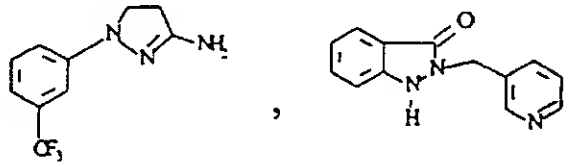
- activity with respect to 5-lipoxygenase: one can cite here the spectrophotometric methods described by Aharony, D. and Stein, R. L. in J. Biol. Chem., 1986, Vol. 261, pp. 11512-11517, and by McMillan, R. M. et al. in Biochim. Biophys. Acta, 1989, Vol. 1005, pp. 170-176.

- activity with respect to cyclo-oxygenases: one can cite here the method that is based on the use of a biological material (epidermis) incubated in the presence of C14 arachidonic acid; the formed hydroxy acids are extracted, separated by HPLC chromatography (Huang, M. et al. in Cancer Res., Vol. 51, pp. 813-819, 1991) or identified by radioimmunoassays (Lysz, T. W. and Needleman, P. J. in Neurochim., Vol. 38, pp. 1111-1117, 1982). One can also mention the test described in the article "Nitric Oxide Activates Cyclo-oxygenase Enzymes, by D. Salvameni et al., Proc. Natl. Sci. USA, Vol. 90, pp. 7240-7244, August, 1993."

The inhibitors of lipoxygenases can be selected notably from redox and non-redox inhibitors, precursors of redox inhibitors, anti-oxidants, iron chelating agents, imidazole compounds, phenothiazines, and benzopyran derivatives as well as certain eicosanoids.

The redox inhibitor can be selected from the catecholic butane derivatives (US-5,008,294, US-4,708,964 and US-4,880,637), such as nordihydroguaiaretic acid (NDGA) or one of its enantiomers such as masoprocol.

The redox inhibitor can also be selected from phenindione, lonapalen, the indazolinones, naphazatrom, benzofuranol, alkylhydroxylamine, and the compounds having the following formulas:



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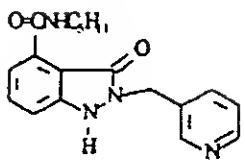


The non-redox inhibitors can be selected from the hydroxythiazoles, the methoxyalkylthiazoles, the benzopyrans and their derivatives, methoxytetrahydropyran, the boswellic acids and their acetylated derivatives, and the quinoline methoxyphenylacetic acids substituted by cycloalkyl radicals.

The anti-oxidant can be selected from the phenols, propyl gallate, the flavonoids and the natural compounds that contain such flavonoids (*Gingko biloba*).

Among the flavonoids that can be used according to the invention, one can cite the hydroxylated derivatives of flavones such as flavonol, dihydroquercetin, luteolin, galangin, and orobol. One can also cite the derivatives of chalcone such as 4,2',4'-trihydroxychalcone, the orthoaminophenols, N-hydroxyureas, the benzofuranols, ebselen and agents susceptible of increasing the activity of the reducing seleno enzymes.

The iron chelating agent can be selected from the hydroxamic acids and their derivatives, the N-hydroxyureas, 2-benzyl-1-naphthol, the catechols, the hydroxylamines, carnosol, naphthol, sulfasalazine, zileuton, 5-hydroxyanthranilic acid and the 4-(ω-arylalkyl)phenylalkanoic acids.

The imidazole compounds can be selected from ketoconazole and itraconazole. [unconfirmed translation].

Among the eicosanoids that are inhibitors of lipoxygenases, one can cite octadecatetraenoic acid, eicosatetraenoic acid, docosapentenoic acid, eicosahexaenoic acid, docosahexenoic acid, and their different esters, as well as various other eicosanoids, possibly in the form of esters, such as PGE1 (prostaglandin E1), PGA2 (prostaglandin A2), viprostol, 15-monohydroxyeicosatetraenoic acid, 15-monohydroxyeicosatrienoic acid and 15-monohydroxyeicosapentenoic acid, and the leukotrienes B5, C5 and D5.

As other various compounds that can inhibit the lipoxygenases, one can also cite products that interfere with calcium flux, particularly the phenothiazines and diphenylbutylamines, verapamil, fuscoside, curcumin, chlorogenic acid, caffeic acid, 5,8,11,14-eicosatetrayenoic acid (ETYA), [sic; -elcosatetraenoic acid] hydroxyphenylretinamide, lonapalene, esculin, diethylcarbamazine, phenanthroline, baicalein, proxicromil, the thio ethers and in particular diallyl sulfide and di-(1-propenyl) sulfide.

The stimulators of lipoxygenases can be especially selected from cytokines such as fibroblast growth factor (FGFβ), transforming growth factor (TGFβ) and epidermal growth factor (EGF).

The inhibitors of cyclo-oxygenases can be especially selected from nonsteroidal anti-inflammatories such as arylcarboxylic derivatives, pyrazole derivatives, oxicam derivatives, and nicotinic acid derivatives.

The stimulators or agonists of cyclo-oxygenases can be especially selected from arachidonic acid metabolites, nitrogen monoxide and the nitrogen monoxide donor compounds, stanozolol, glutathione donor compounds, neuropeptides and, in particular,

vasoactive intestinal peptide (V.I.P.), calcium ionophores, anthocyanosides, bioflavonoids, FGA, and platelet activating factors (PAF).

Finally, among the substances that can be used both as inhibitor of lipoxygenases and stimulator of cyclo-oxygenases, one can cite, in particular, 6-chloro-2,3-dihydroxy-1,4-naphthoquinone (CNDQ).

Now, concerning the substrates that are suitable for lipoxygenases and cyclo-oxygenases, one can cite polyunsaturated fatty acids, particularly those containing 20 carbon atoms, such as arachidonic acid, dihomo-γ-linolenic acid or eicosapentanoic acid.

As precursors of such substrates, one can, more particularly, cite the so-called essential polyunsaturated fatty acids, such as linoleic acid, α-linolenic acid and γ-linolenic acid, as well as cell membrane phospholipids such as phosphatidylserine, phosphatidylethanolamine, phosphatidylcholine, phosphatidylinositol and diphosphatidylglycerol.

The substrates, or precursors of substrates, mentioned above can be obtained especially from certain natural compounds, particularly certain foods of animal, plant or microbial origin (plant oil extracts such as the oil of *Oenothera biennis*, borage oil, blackcurrant seed oil, oenothera oil, fish oil extracts, insect tissue oil extracts).

According to the invention, it is naturally possible to directly use such natural compounds that contain the desired substrates and/or the precursors of substrates. It is also possible to use products obtained by industrial synthesis.

Finally, it should be noted in general that, in the context of the present invention, it is clearly absolutely possible to use mixtures of inhibitors, mixtures of stimulators, mixtures of substrates, mixtures of precursors, as well as mixtures of these mixtures, provided that these mixtures of mixtures remain compatible with the desired effect.

Next the description of the method of the invention is continued in greater detail.

As indicated above, this method essentially consists of administering to the organism, by a topical and/or systemic route, at least one inhibitor or at least one stimulator of lipoxygenases or of cyclo-oxygenases, said administration taking place preferably in combination (simultaneously, separately or spread out over time) with at least one substrate, or one precursor of a substrate, as defined above.

It is preferred for the inhibitors and the stimulators of enzymes to be administered by the topical route.

As far as the substrates and/or their precursors are concerned, they can be administered either by the systemic route, and in this case preferably by the oral route, or more preferably by the topical route.

According to a particularly preferred embodiment of the method according to the invention, compositions for topical use are applied to the skin and/or scalp; these compositions jointly contain the inhibitors and/or the stimulators of enzymes on one hand, and the substrate and/or their precursors on the other hand.

In general, it should be noted that all the above products can be packaged in the standard manner, in a form suitable for

the chosen administration or application procedure for the latter (lotions, shampoos, tablets, creams and others).

The compositions or the kits that fall within the context of the present invention are more particularly the following:

- the compositions (A) comprising at least one inhibitor of lipoxygenases and at least one stimulator of cyclo-oxygenases,
- the compositions (B) comprising at least one inhibitor of cyclo-oxygenases and at least one stimulator of lipoxygenases,
- the compositions (C) comprising at least one inhibitor of lipoxygenases and/or at least one stimulator of cyclo-oxygenases, in association with at least one substrate for lipoxygenases and cyclo-oxygenases and/or one precursor of such a substrate,
- the compositions (D) comprising at least one inhibitor of cyclo-oxygenases and/or at least one stimulator of lipoxygenases, in association with at least one substrate for lipoxygenases and cyclo-oxygenases and/or one precursor of such a substrate,
- the kits (E) comprising in a first compartment at least one inhibitor of lipoxygenases and, in a second compartment, at least one stimulator of cyclo-oxygenases,
- the kits (F) comprising in a first compartment at least one inhibitor of cyclo-oxygenases and, in a second compartment, at least one stimulator of lipoxygenases,
- the kits (G) comprising in a first compartment at least one inhibitor of lipoxygenases and/or one stimulator of cyclo-oxygenases or conversely at least one inhibitor of cyclo-oxygenases and/or at least one stimulator of lipoxygenases, and, in a second compartment, at least one substrate for lipoxygenases and cyclo-oxygenases and/or at least one precursor of such a substrate.

As indicated above, each one of the compositions (A), (B), (C) and (D), as well as each one of the components put in the compartments of the kits (E), (F) and (G) are packaged in the standard manner, in a form suitable for the different procedures of administration or application considered for the latter (lotions, shampoos, tablets, creams and others). Thus, the compositions (A)-(D) and the kits (E)-(F) are preferably packaged in a form suitable for a topical application, and in the context of the kits (G), the components of the first compartment are preferably packaged in a form adapted for topical application, whereas the components of the second compartment are packaged in a form adapted for administration by the oral route.

In general, according to the present invention, it is in fact possible to design presentation kits containing as many separate compartments as there are substances one wishes to use or which should be used (inhibitors, stimulators, substrates, precursors of substrates).

The compositions according to the invention, or the kits according to the invention, or the implementation of the method according to the invention, can also use different standards and usual additives, particularly cosmetic additives in the case of topical applications (notably hair-care products), selected from, for example, UV filters, thickeners, penetration agents such as urea, organic solvents such as ethanol, isopropanol, alkylene glycols, surfactants selected from nonionic surfactants such as alkyl polyglycosides, cationic surfactants, anionic surfactants and amphoteric surfactants, dyes, antidandruff agents, perfumes and preservatives.

It is also possible to integrate in the composition according to the invention products that in themselves are

already known and that present activity in the field of fur and/or hair growth, such as, for example, 2,4-diamino-6-piperidinopyrimidine-3-oxide marketed especially under the trade name "Minoxidil" by the company UPJOHN.

To obtain notable effects, the frequency of administration or application of the compositions according to the invention, both with and without substrate or precursor of substrate, is on the order of one to two times per day. In this regard, it has been noted that the sufficient quantities of inhibitory and/or stimulatory agents to be used in the context of the invention can, generally, remain very small.

The present invention has applications particularly in the field of the treatments of various pathologies affecting the skin and/or scalp, particularly hirsutism and alopecia, notably iatrogenic alopecia.

Concrete examples illustrating the invention will now be given.

Example 1: Unrinsed lotion

NDGA	0.1 g
Linoleic acid	0.1 g
Propylene glycol	22.8 g
Ethanol 95°	55.1 g
Purified water	qsp 100 g

Example 2: Unrinsed lotion

NDGA	2 g
Linoleic acid	5 g
Propylene glycol	22.8 g
Ethanol 95°	55.1 g
Purified water	qsp 100 g

Example 3: Rinsed lotion

NDGA	5 g
Linoleic acid	5 g
Propylene glycol	22.8 g
Ethanol 95°	55.1 g
Purified water	qsp 100 g

Example 4: Rinsed lotion

NDGA	8 g
Linoleic acid	15 g
Propylene glycol	22.8 g
Absolute ethanol	qsp 100 g

Example 5: Shampooing

NDGA	1 g
Linoleic acid	1 g
Surfactant APG 300 15 g MA [active matter]	(=30 g)
Purified water	qsp 100 g

Example 6: Unrinsed lotion

Gingko biloba (1)	5 g
Propylene glycol	22.8 g
Ethanol 95°	55.1 g
Purified water	qsp 100 g

(1): flavonoid-rich natural extract

Example 7: Unrinsed lotion

Ketoconazole	0.5 g
Propylene glycol	22.8 g
Ethanol 95°	55.1 g
Purified water	qsp 100 g

Example 8: Unrinsed lotion

Diallyl sulfide	11.4 g
Propylene glycol	22.8 g
Ethanol 95°	55.1 g
Purified water	qsp 100 g

Example 9: Unrinsed lotion

Gingko biloba	5 g
Linoleic acid	5 g
Propylene glycol	22.8 g
Ethanol 95°	55.1 g
Purified water	qsp 100 g

Example 10: Unrinsed lotion

Ketoconazole	0.5 g
Linoleic acid	5 g
Propylene glycol	22.8 g
Ethanol 95°	55.1 g
Purified water	qsp 100 g

Example 11: Unrinsed lotion

Diallyl sulfide	11.4 g
Linoleic acid	5 g
Propylene glycol	22.8 g
Ethanol 95°	55.1 g
Purified water	qsp 100 g

Example 12: Unrinsed lotion

Gingko biloba	5 g
Borage oil[(2)]	10 g
Propylene glycol	22.8 g
Ethanol 95°	55.1 g
Purified water	qsp 100 g

[(2)]: natural extracts containing the polyunsaturated fatty acid 18:2n-6 and 18:3n-6

Example 13: Unrinsed lotion

CDNQ	2 g
Linoleic acid	5 g
Propylene glycol	22.8 g
Ethanol 95°	55.1 g
Purified water	qsp 100 g

Example 14: Unrinsed lotion

CDNQ	2 g
Borage oil	10 g
Propylene glycol	22.8 g
Ethanol 95°	55.1 g
Purified water	qsp 100 g

Example 15: Unrinsed lotion

Indomethacin	0.25 g
Propylene glycol	22.8 g
Ethanol 95°	55.1 g
Purified water	qsp 100 g

Example 16: Unrinsed lotion

Indomethacin	0.25 g
Docosahexaenoic acid	2 g
Propylene glycol	22.8 g
Ethanol 95°	55.1 g
Purified water	qsp 100 g

All the compositions 1-14 listed above produced good results in the growth of fur and hair, particularly those containing a substrate or a precursor of a substrate for lipoxygenases and cyclo-oxygenases. Examples 15 and 16, on the other hand, produced good results in slowing down the growth of fur and hair.

Claims

1. Treatment method for modifying the growth of fur and/or hair, characterized in that it consists in administering to the organism, by a topical and/or systemic route, at least one inhibitor or at least one stimulator of lipoxygenases or of cyclo-oxygenases.

2. Method according to Claim 1 to promote the growth and/or to limit the loss of fur and/or hair, characterized in that at least one inhibitor of lipoxygenases and/or at least one stimulator of cyclo-oxygenases is/are used.

3. Method according to Claim 2, characterized in that at least one inhibitor of lipoxygenases and at least one stimulator of cyclo-oxygenases is/are used.

4. Method according to Claim 3, characterized in that at least one substance is used that is both an inhibitor of lipoxygenases and a stimulator of cyclo-oxygenases.

5. Method according to Claim 1 to slow down and/or prevent the loss of fur and/or hair, characterized in that at least one stimulator of lipoxygenases and/or at least one inhibitor of cyclo-oxygenases is used.

6. Method according to Claim 5, characterized in that at least one stimulator of lipoxygenases and at least one inhibitor of cyclo-oxygenases is used.

7. Method according to Claim 6, characterized in that at least one substance is used that is both a stimulator of lipoxygenases and an inhibitor of cyclo-oxygenases.

8. Method according to any one of the preceding claims, characterized in that the inhibitors and the stimulators of lipoxygenases or of cyclo-oxygenases are administered by a topical route.

9. Method according to any one of the preceding claims, characterized in that at least one substrate for lipoxygenases and cyclo-oxygenases and/or at least one precursor of a substrate for lipoxygenases and cyclo-oxygenases is taken in by the organism by a topical and/or systemic route.

10. Method according to Claim 9, characterized in that said intake of substrate or precursor of substrate is carried out simultaneously, separately or spread out over time, in comparison to the step of the administration of inhibitors or stimulators of lipoxygenases or of cyclo-oxygenases.

11. Method according to one of Claim 9 or 10, characterized in that said intake is by an oral and/or topical route.

12. Method according to Claim 11, characterized in that said intake is by a topical route.

13. Method according to Claim 12, characterized in that it consists in using a composition for topical use containing both the inhibitors or stimulators of lipoxygenases or of cyclo-oxygenases on the one hand and the substrates or precursors of substrates for lipoxygenases and cyclo-oxygenases on the other hand.

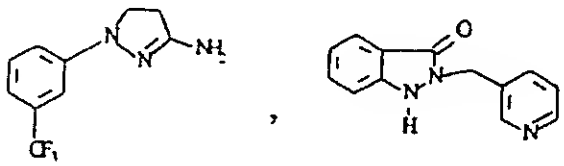
14. Method according to any one of the preceding claims, characterized in that used inhibitors of lipoxygenases are selected from redox and non-redox inhibitors, precursors of redox

inhibitors, antioxidants, iron chelating agents, imidazole compounds, phenothiazines, derivatives of benzopyran, eicosanoid inhibitors, products that interfere with calcium flux and, in particular, phenothiazines and diphenylbutylamines, verapamil, fuscoside, curcumin, chlorogenic acid, caffeic acid, 5,8,11,14-eicosatetrayenoic acid (ETYA), hydroxyphenylretinamide, lonapalene, esculin, diethylcarbamazine, phenanthroline, baicalein, proxicromil, thio ethers and, in particular, diallyl sulfate and di-(1-propenyl) sulfide.

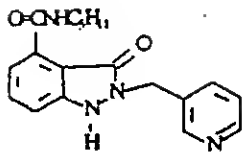
15. Method according to Claim 14, characterized in that the redox inhibitors are selected from the derivatives of catecholic butanes.

16. Method according to Claim 15, characterized in that the derivatives of catecholic butanes are selected from the nordihydroguaiaretic acid (NDGA), masoprocol.

17. Method according to Claim 14, characterized in that the redox inhibitors are selected from phenidone, ianopalen, indazolinones, naphazatrom, benzofuranol, alkylhydroxylamine, and the compounds having the following formulas:



and



18. Method according to Claim 14, characterized in that the nonredox inhibitors are selected among the hydroxythiazoles, methoxyalkylthiazoles, benzopyrans and their derivatives, methoxytetrahydropropyran, the boswellic acids and their acetylated derivatives, and the quinoline methoxyphenylacetic acids substituted with cycloalkyl radicals.

19. Method according to Claim 14, characterized in that the antioxidants are selected from the phenols, propyl gallate, the flavonoids and/or the natural compounds containing such flavonoids, particularly the hydroxylated derivatives of flavones, such as flavonol, dihydroquercetin, luteolin, galangin, orobol, the derivatives of chalcone such as 4,2',4'-trihydroxychalcone, the orthoaminophenols, the N-hydroxyureas, the benzofuranols, ebselen and agents susceptible of increasing the activity of reducing seleno enzymes.

20. Method according to Claim 14, characterized [in that] the iron chelating agents are selected from the hydroxamic acids and their derivatives, the N-hydroxyureas, 2-benzyl-1-naphthol, the catechols, hydroxylamines, carnosol, naphthol, sulfasalazine, zileuton, 5-hydroxyanthranilic acid and the 4-(ω-arylalkyl)phenylalkanoic acids.

21. Method according to Claim 14, characterized in that the imidazole compounds are selected from ketoconazole and itraconazole.

22. Method according to Claim 14, characterized in that the eicosanoid inhibitors are selected from octadecatetraenoic acid, eicosatetraenoic acid, docosapentenoic acid, eicosahexaenoic acid, docosahexenoic acid and their different esters, as well as various other eicosanoids, possibly in the form of esters, such as PGE1 (prostaglandin E1), PGA2 (prostaglandin A2), viprostol, 15-monohydroxyeicosatetraenoic acid, 15-monohydroxyeicosatrienoic acid and 15-monohydroxyeicosapentenoic acid, and the leukotrienes B5, C5 and D5.

23. Method according to any one of the preceding claims, characterized in that used inhibitors of cyclo-oxygenases are selected from nonsteroidal anti-inflammatories.

24. Method according to Claim 23, characterized in that the nonsteroidal anti-inflammatories are selected from arylcarboxylic derivatives, pyrazole derivatives, oxicam derivatives, and nicotinic acid derivatives.

25. Method according to any one of the preceding claims, characterized in that the used stimulators or agonists of cyclo-oxygenases are selected from arachidonic acid metabolites, nitrogen monoxide and nitrogen monoxide donor compounds, stanozolol, glutathione donor compounds, neuropeptides and in particular V.I.P., calcium ionophores, anthocyanosides, bioflavonoids, FGA, and platelet activating factors (PAF).

26. Method according to any one of the preceding claims, characterized in that the used stimulators of lipoxygenases are selected from cytokines such as FGFβ, TGFβ and epidermal growth factor (EGF).

27. Method according to any one of the preceding claims, characterized in that as substance acting both as an inhibitor of the lipoxygenáses and a stimulator of the cyclo-oxygenases, 6-chloro-2,3-dihydroxy-1,4-naphthoquinone (CNDQ) is used.

28. Method according to any one of Claims 9-27, characterized in that the used substrates for lipoxygenases and cyclo-oxygenases are selected from the fatty polyunsaturated acids , particularly those containing 20 carbon atoms.

29. Method according to Claim 28, characterized in that said fatty polyunsaturated acids are selected, alone or in mixtures, from arachidonic acid, dihomo-γ-linolenic acid and eicosapentaenoic acid.

30. Method according to any one of Claims 9-29, characterized in that precursors of substrates for lipoxygenases and cyclo-oxygenases are used which are selected from the essential fatty acids and the cell membrane phospholipids.

31. Method according to Claim 30, characterized in that said essential fatty acids are selected, alone or in mixtures, from linolenic acid, α-linolenic acid and β-linolenic acid.

32. Method according to Claim 30, characterized in that said phospholipids are selected, alone or in mixtures, from phosphatidylserine, phosphatidylethanolamine, phosphatidylcholine, phosphatidylinositol and diphosphatidylglycerol.

33. Compositions, characterized in that they comprise at least one inhibitor of lipoxygenases associated with at least one stimulator of cyclo-oxygenases or, conversely, at least one inhibitor of cyclo-oxygenases associated with at least one stimulator of lipoixygenases.

34. Compositions characterized in that they comprise at least one substrate for lipoxygenases and cyclo-oxygenases and/or a precursor of a substrate for lipoxygenases and cyclo-oxygenases, in association with at least one inhibitor of lipoxygenases and/or at least one stimulator of cyclo-oxygenases or, conversely, at least one inhibitor of cyclo-oxygenases and/or at least one stimulator of lipoxygenases.

35. Compositions according to one of Claim 33 or 34, characterized in that they are packaged in a form suitable for a topical application.

36. Compositions according to any one of Claims 33-35, characterized in that the inhibitors, the stimulators, the substrates and the precursors of substrates of the enzymes lipoxygenase and cyclo-oxygenase are as defined in Claims 14-32.

37. Device with several compartments or kits, characterized in that they comprise in a first compartment at least one inhibitor of lipoxygenases, or, conversely, at least one inhibitor of cyclo-oxygenases and, in a second compartment, at least one stimulator of cyclo-oxygenases or, conversely, at least one stimulator of lipoxygenases.

38. Kits according to Claim 37, characterized in that the compounds put in said first and second compartments are packaged in the form suitable for a topical application.

39. Devices with several compartments or kits, characterized in that they comprise in a first compartment at least one inhibitor of lipoxygenases and/or at least one stimulator of cyclo-oxygenases or, conversely, at least one inhibitor of cyclo-oxygenases and/or at least one stimulator of lipoxygenases, and in a second compartment at least one substrate for lipoxygenases

and cyclo-oxygenases and/or one precursor of a substrate for lipoxygenases and cyclo-oxygenases.

40. Kits according to Claim 39, characterized in that the compounds put in said first compartment are packaged in a form suitable for a topical application, and the compounds put in said second compartment are packaged in a form suitable for administration by an oral route or administration by a topical route.

41. Kits according to one of Claim 39 or 40, characterized in that the inhibitors, the stimulators, the substrates and the precursors of substrates of the enzymes lipoxygenase and cyclo-oxygenase are as defined in Claims 14-32.

42. Use of an inhibitor or of a stimulator of lipoxygenases or of cyclo-oxygenases, as an agent to modify the growth of fur and/or hair.

43. Use according to Claim 42 of an inhibitor of lipoxygenases and/or of a stimulator of cyclo-oxygenases, as an agent(s) to promote the growth and/or limit the loss of fur and/or hair.

44. Use according to Claim 42 of a stimulator of lipoxygenases and/or of an inhibitor of cyclo-oxygenases, as agent(s) to slow down and/or prevent the growth of fur and/or hair.

45. Use according to one of Claims 42-44, characterized in that said inhibitors or stimulators of lipoxygenases and of cyclo-oxygenases are used by means of compositions or of kits as defined in any one of Claims 33-41.

European Patent Office

Application Number

EP 94 40 2055

EUROPEAN SEARCH REPORT

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int Cl[5])
X	CONTEMP. REV. OBSTET. GYNAECOL., vol.4, no.2, 1992 pages 90 - 101 Z.M. VAN DER SPUY 'Management of hyperandrogenism.' * page 95 * ---	1,5,14, 21,42,44	A61K31/00 A61K31/05 A61K31/495 A61K31/095 A61K31/12 A61K31/405 A61K35/78
X	FR-A-2 380 775 (SEDERMA SARL) September 15, 1978 ---	1,9,28, 31	A61K7/06
P,X	J. PHARM. SOC. JPN, vol.113, no.10, 1993 pages 718 - 724 N. KOBAYASHI ET AL. 'Effect of leaves of Ginko biloba on hair regrowth in C3H strain mice.' * Abstract * ---	1,5,14, 19,42,43	
A	J. LIPID RES., vol.34, no.9, 1993 pages 1505 - 1514 A.N. BAER ET AL. 'Fatty acid oxygenase activity of human hair roots.' -----		

TECHNICAL FIELDS SEARCHED (Int Cl[5])

A61K

The present search report has been drawn up for all claims.

Place of search	Date of completion of the search	Examiner
THE HAGUE	October 19, 1994	Klaver, T

CATEGORY OF CITED DOCUMENTS

X: Particularly relevant if taken alone.
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A: Technological background.
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T: Theory or principle inderlying the invention.
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D: Document cited in the application.
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